Sustained release lithium carbonate tabl ts

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Abstract

Sustained release lithium carbonate tablets are made by micronising lithium carbonate, mixing it with dry filler and binding agent, adding a solution of glyceryl mono-, di-, and tri- esters, of C16-18 saturated fatty acids, adding to the mixture water in an amount of <100>/3 &cirf& 36x litres per 100 gs. lithium carbonate where x is the particle size in microns of the micronised lithium carbonate, and then moist- granulating and screening the mass, and compressing the resulting granules into tablets.

12

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(54) Sustained release lithium carbonate tablets

(57) Sustained release lithium carbonate tablets are made by micronising lithium carbonate, mixing it with dry filler and binding agent, adding a solution of glyceryl mono-, di-, and tri-esters, of C16-18 saturated fatty acids, adding to the mixture water in an amount of $^{100}/_{3.36x}$ litres per 100 gs. lithium carbonate where x is the particle size in microns of the micronised lithium carbonate, and then moist-granulating and screening the mass, and compressing the resulting granules into tablets.

GB 2 016 922 A

SPECIFICATION

Method of making sustained release tablets

This invention relates to a method of manufacture of sustained release lithium carbonate tablets.

In our Patent Specification 1 450 536 we have described and claimed a method of making a sustained release lithium carbonate pharmaceutical tablet in which a mixture of powdered lithium carbonate and one or more excipients is coated with a mixture of glyceryl mono-, di- or tri- esters of one of more C_{16}-C_{18} straight chain saturated fatty acids and formed into tablets after granulation by a moist granulation technique characterised in that a certain quantity of water is used per 100 kg of lithium carbonate, the quantity of water being based on the bulk density of the lithium carbonate and that, prior to compaction into tablets, the granules are screened to form a granulate whose particles are substantially all less than 12BS Mesh, from 20 to 30% of which have particle sizes in the range of from 12BS Mesh to 60 BS Mesh and from 70 to 80% of which have a particle size below 60BS Mesh.

This method is entirely satisfactory as long as the lithium carbonate is homogeneous in the sense of being either an amorphous substance or a crystalline material of homogeneous structure.

In the recent past we have been receiving lithium carbonate from another source and this appeared to have entirely different properties to the previous homogeneous material. On examination of the new material it was found to contain a crystalline material some of which comprised needle shaped crystals and some of which was cuboid.

When the new material was dealt with in the way described in Patent Specification 1 450 536 it was found that consistent results were not achieved, and the necessity arose to arrive at some other method of consistent formulation.

Having failed to operate satisfactorily on the basis of the method set out in our prior application, our first thoughts lay in the direction of milling the material in order to try to reduce it to a constant size and shape. Unfortunately it proved impossible to achieve a satisfactory material by conventional milling, as the carbonate was impacted and bulk density of the material adversely affected, altering specific area criteria.

We have however found that it is possible to comminute the lithium carbonate material by means of a micronisation technique. This produces the lithium carbonate in fine powder form, the powder grains having a sufficiently constant surface area to enable consistent formulation of the delayed release tablets.

Having solved the problem of dealing with crystals of different structure by the micronisation technique, we were able to take the matter one stage further. By specifying micronisation to a specific particle size, it is possible to avoid altogether the separate step of measurement of bulk density, since one is then dealing with particles of given size and shape; thus, for any particular particle size, one knows that a specific water content is required per given weight of lithium carbonate.

The amount of water which must be added to the lithium carbonate may be calculated according to the following formula:

$$Y = \frac{100}{Kx}$$

where Y is the number of litres of water to be added per 100 Kg of the micronised lithium carbonate,
K is a constant equal to 3.36; and
x is the particle size in microns.

Translated into terms of particle size, the amount of water to be added per 100 kg of the micronised lithium carbonate is shown below for the grain sizes given.

Particle Size	*Amount of water to be added*
1.75 µm	17.0 litres
2.25 µm	13.2 litres
2.75 µm	10.8 litres
3.25 µm	9.2 litres
3.75 µm	7.95 litres
4.25 µm	7.0 litres

These quantities should be adhered to rather strictly though a small tolerance in the amount of water added (say ± 10%) is permissible.

Apart from the step of micronisation and the calculation of the amount of water to be added based on the micronisation size, the process steps set out in our prior application apply equally as before.

Thus, according to the present invention, we provide a method of making a sustained release lithium carbonate pharmaceutical tablet in which a mixture of lithium carbonate and one or more excipients is coated with a mixtur of glyceryl m no-, di- and tri-esters of one or more C_{16}-C_{18} straight chain saturated fatty acids and formed into tablets by a moist granulation technique characterised in that before mixing with

excipients the dry powdered lithium carbonate is micronised to a specified particle size, that the amount of water used corresponds to about $^{100}/_{3.36x}$ litres per 100 kg lithium carbonate where x is the grain size of the lithium carbonate powder in microns and that, prior to compaction into tablets, the granules are screened to form a granulate whose particles are substantially all less than 12BS Mesh, from 20 to 30% of which have particle sizes in the range of from 12BS Mesh to 60 BS Mesh and from 70 to 80% of which have a particle size below 60BS Mesh.

The excipients may include a filler such as mannitol, a binding agent such as gum acacia, and a lubricant such as magnesium stearate.

A preferred process comprises the steps of micronising dry powdered lithium carbonate to a specified particle size, mixing the micronised lithium carbonate with a dry powdered filler and with a dry binding agent, mixing therewith a solution of a mixture of glyceryl mono-, di- and tri-esters of one or more C_{16}-C_{18} straight chain saturated fatty acids, adding an amount of water corresponding to about $^{100}/_{3.36x}$ litres per 100 kg lithium carbonate where x is the grain size of the lithium carbonate powder in microns, kneading the mixture, drying the resultant mass, screening the granules to form a granulate whose particles are substantially all less than 12BS Mesh, from 20 to 30% of which have particle sizes in the range of from 12BS Mesh to 60BS Mesh and frm 70 to 80% of which have a particle size below 60BS Mesh, and compressing the granulate into tablets.

Preferably 25% of the particles of said granulate have particle sizes in the range of from 12BS Mesh to 60 BS Mesh and 75% of the particles have a particle size below 60BS Mesh. For details of the sieve sizes reference should be made to British Standard No. 410/62.

The mixture of glyceryl esters preferably contains less than 25% by weight of mono-esters. Preferably it contains not more than about 50% by weight of di-esters, the balance being tri-esters. A typical mixture is sold under the trade name Precirol by Messrs Gattefosse of France. It is prepared from palmitostearic acids having the approximate composition by weight: stearic acid 46.5%, palmitic acid 51%, lauric acid 2%, and traces of myristic and oleic acids. The final ester composition by weight is mono-ester 12.17%, di-ester 43-47%, and tri-ester 35-44%, there being less than 1% free glycerol. it is important that the mixture contains principally C_{16}-C_{18} straight chain saturated fatty acids. In practice, since acids are normally obtained from natural sources, a mixture will contain principally palmitic and stearic acids, and small amounts of other acids having fewer than 16 or more than 18 carbon atoms may be present. It is to be understood that minor amounts of such other acid radicals may be present in quantities which do not significantly affect the sustained release function of the mixture of glyceryl esters.

Preferably the tablets contain frm 9.5 to 11.4 parts by weight of the mixture of glyceryl esters per 100 parts by weight of lithium carbonate, that is to say from 51 to 61 parts of the mixture of glyceryl esters per 100 parts of therapeutically active lithium.

A lubricant, such as magnesium stearate, may be added to the granulate after screening and before tableting.

Preferably the mixture of glyceryl esters is added in alcoholic solution and at an elevated temperature such as 68° or above, and preferably at a temperature of 7248C, in which case the mixture of powdered lithium carbonate and filler are desirably pre-heated to about this temperature before the solution is added, preferably to a temperature of 70°C. Preferably kneading is carried out for a period of from about 10 to 20 minutes. The mixture is preferably dried at a slightly elevated temperature, for example at a temperature of from 30 to 50°C, preferably 40°C.

Screening is preferably carried out in a conventional sieve analysis apparatus using sieves having gradually decreasing mesh openings, for example sieves of 12BS Mesh, 16BS Mesh, 22BS Mesh, 30BS Mesh and 60BS Mesh. After a particular batch has been graded the various fractions retained on the sieves are blended one with another and, if necessary, with material from a preceding or subsequent batch so as to form a granulate having the desired particle size.

The granulate is then compressed into tablets, preferably on a rotary tabletting machine. Desirably the tablets have a Monsanto hardness of 4.

The invention is illustrated in the following example.

EXAMPLE

Powdered lithium carbonate of pharmaceutical quality (BP 1968) purchased from Foote Mineral Company Limited, was micronised to a powder having a particle size of 2.75 μm. 16.5 kg of powdered mannitol BP were sieved through a 25BS Mesh screen and the sieved material was then placed with 100 kg of the powdered lithium carbonate in a mixer together with 5 kg of dried gum acacia. The mixer had a jacket for heating by steam or hot water and possessed a horizontal mixer shaft bearing four Z-shaped blades. The temperature was measured by means of a metal encased thermometer dipping at least six inches into the powder. Mixing and controlled heating were continued until a uniform temperature of 70°C was attained and held for 15 minutes.

The mixture of glyceryl esters used for the purpose of this example is that sold under the trade name Precirol by Messrs. Gattefosse of France. 9.75 kg of Precirol were dissolved in 40 litres of 96% alcohol and the temperature of the solution was brought to 72°C whereupon it was poured onto the heated powdered mixture of mannitol, gum acacia and lithium carbonate and mixed for 15 minutes.

The calculated quantity of water, (i.e. 10.8 litres), was then poured onto the mixture and the whole mass

was knead d. The resulting mass was then dried at 40°C by evaporation, e.g. in an Aeromatic dryer. The crude granulate was then passed through a 12BS Mesh sieve and submitted to a sieve analysis using si ves f 12BS Mesh, 16BS Mesh, 22BS Mesh, 30BS Mesh and 60 BS Mesh. Approxmately 110 kg of granulate passed the 60BS Mesh. Approximately 6.0 kg was retained on the 16BS Mesh, approximately 4.5 kg on the 22BS Mesh, approximately 6.0 kg on the 30BS Mesh sieve and 6.4 kg on the 60BS Mesh sieve.

Since the proportion of particles in the 12 and 60BS Mesh range was less than one quarter the weight of the particles passing the 60BS Mesh sieve, the balance was adjusted by adding 13.0 kg of material which was retained on the 22BS Mesh sieve from an earlier batch. The particles below 60BS Mesh were then intimately blended with the resulting mixture of particles in the 12 and 60BS Mesh range. 5 kg of wheat starch and 1.25 kg magnesium stearate was then added and mixed with the dried granulate. The resulting mixture was then compressed into tablets on a rotary tabletting machine with flat, cup-shaped and rod-shaped punches. The resulting tablets had a weight of about 551 milligrams, a Monsanto hardness of 6.0 kg and contained about 400 milligrams of lithium carbonate and 39.0 milligrams of Precirol.

CLAIMS

1. A method of making a sustained release lithium carbonate pharmaceutical tablet in which a mixture of lithium carbonate and one or more excipients is coated with a mixture of glyceryl mono-, di- and tri-esters of one or more C_{16}-C_{18} straight chain saturated fatty acids and formed into tablets by a moist granulation technique characterised in that before mixing with the excipients the dry powdered lithium carbonate is micronised to a specified particle size, that the amount of water used corresponds to about $^{100}/_{3.36x}$ litres per 100 kg lithium carbonate where x is the grain size of the lithium carbonate powder in microns and that, prior to compaction into tablets, the granules are screened to form a granulate whose particles are substantially all less than 12BS Mesh, from 20 to 30% of which have particle sizes in the range of from 12BS Mesh to 60 BS Mesh and from 70 to 80% of which have a particle size below 60BS Mesh.

2. A method of manufacturing sustained release lithium carbonate tablets which comprises the steps of micronising dry powdered lithium carbonate to a specified particle size, mixing the micronised lithium carbonate with a dry powdered filler and with a dry binding agent, mixing therewith a solution of a mixture of glyceryl mono-, di- and tri-esters of one or more C_{16}-C_{18} straight chain saturated fatty acids, adding an amount of water corresponding to about $^{100}/_{3.36x}$ litres per 100 kg lithium carbonate where x is the grain size of the lithium carbonate powder in microns, kneading the mixture, drying the resultant mass, screening the granules to form a granulate whose particles are substantially all less than 12BS Mesh, from 20 to 30% of which have particle sizes in the range of from 12BS Mesh to 60BS Mesh and from 70 to 80% of which have a particle size below 60BS Mesh, and compressing the granulate into tablets.

3. A method according to claim 1 or claim 2 wherein about 25% of the particles of the said granulate have particle sizes in the range of from 12BS Mesh to 60BS Mesh and about 75% of the particles have a particle size below 60BS Mesh.

4. A method according to any one of the preceding claims wherein the mixture of glyceryl esters contains less than 25% by weight of mono-esters.

5. A method according to any one of the preceding claims wherein the mixture of glyceryl esters contains not more than about 50% by weight of di-esters.

6. A method according to any one of the preceding claims wherein the tablets contain from 9.5 to 11.4 parts by weight of the mixture of glyceryl esters per 100 parts by weight of lithium carbonate.

7. A method according to any one of the preceding claims wherein a lubricant is added to the granulate after screening and before tabletting.

8. A method according to any one of the preceding claims wherein the mixture of glyceryl esters is added in alcoholic solution at temperature of 68°C or higher.

9. A method according to claim 8 wherein the mixture of powdered lithium carbonate and filler is pre-heated before adding the said solution.

10. A method according to any one of the preceding claims wherein the granulate is compressed into tablets on a rotary tabletting machine to give a Monsanto hardness of about 4.

11. A method of making a sustained release lithium carbonate pharmaceutical tablet substantially as herein described with reference to the Example.

12. A sustained release lithium carbonate pharmaceutical tablet made by the method of any one of the preceding claims.

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